# EFFECTS OF STRESS AND KINDLING PARADIGMS ON NEUROPEPTIDE GENE EXPRESSION: FOCUS ON CORTICOTROPIN RELEASING HORMONE

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Corticotropin releasing hormone (CRH) when administered icv to animals causes a coordinated behavioral response characterized by heightened arousal and motor activation similar to that produced by stress. This raises the possibility that CRH, which is distributed throughout the limbic system, may contribute to the behavioral activation and anxiety induced by stress. Consistent with this hypothesis we have found that stress and icv CRH induces the transcription factor, c-fos, in many of the same brain areas including the piriform cortex and dentate gyrus. In order to address the role of extrahypothalamic CRH in mediating behavioral responses to stress, we have turned to limbic kindling as a model. In kindling, a subconvulsive electrical (or pharmacological e.g. cocaine) stimulus applied daily eventually results in generalized seizures. Moreover, electrical kindling of the amygdala increases the vulnerability to stress-induced ulcers and potentiates defensive fighting induced by CRH. Because icv CRH produces limbic seizures which cross-sensitize with amygdala kindled seizures, we investigated whether CRH might be induced during kindling and contribute to the limbic hyperexcitability.

Amygdala kindling, resulting in either afterdischarges alone or full-blown seizures, induced CRH mRNA and CRH-like immunoreactivity in the hippocampal formation where normally very little CRH occurs. Both the number of cells expressing CRH and the amount of CRH mRNA per cell were increased at 24 h but not at 3 weeks after the last stimulus. Amygdala kindling also induced CRH-binding protein mRNA. CRH and CRH-BP were induced almost exclusively in GABAergic interneurons in the dentate hilus. Other neuropeptides including somatostatin and NPY were induced by kindling and co-localized with CRH.

Co-localization of CRH and GABA in the dentate hilus is intriguing given the fact that GABAergic drugs and benzodiazepines reverse many of the anxiogenic properties of CRH and inhibit CRH release. We are currently investigating interactions between CRH and GABA in the regulation of neuronal activity in the dentate gyrus. Whether CRH acts as a neurotransmitter or alternatively as a neurotrophic factor is unknown. Nevertheless these findings support a role for CRH in modulating neuronal excitability in the limbic system and also raise the possibility that CRH-induced limbic hyperarousal may be relevant to the increased vulnerability to psychopathology associated with recurrent stress.